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THE PLAGUE SITUATION.

PORTO RICO.

From August 14 to 20, both dates inclusive, there was only 1 case of plague reported in Porto Rico. This case occurred in San Juan and was reported as suspicious on August 14. The diagnosis of plague was established August 16. This makes a total of 49 cases reported in all Porto Rico up to August 20. Of these, 33 occurred in San Juan.

The disease seems to be well under control, there having been only 2 cases since the 1st of August. The work of eradicating the infection among rodents, however, still remains. This will take some time, as it necessarily includes the poisoning and trapping of rats over a sufficiently long period to markedly reduce their numbers and the general ratproofing of all buildings which might otherwise harbor rodents. Both the destruction of rats and the ratproofing of buildings have been under way for some time.

CUBA.

In Cuba there have been in all 3 cases of plague in Habana. The last case was reported on July 22, and the last death July 27. It is a month since any case has developed.

The restrictions placed upon passengers coming from Habana to the United States, therefore, have been removed excepting as regards persons who have resided in Habana between Cuba Street and the water front. The restrictions on vessels and cargoes directed against the importation into the United States of infected rodents remain unchanged.

The work of trapping and poisoning rats continues, and the rats collected are being examined to ascertain whether plague infection exists among them. From June 24 to August 10, 6,216 rats had been examined in this way without the finding of any infected with plague.

ACTIVE AND PASSIVE IMMUNIZATION AGAINST PLAGUE.

By Wade H. Frost, Passed Assistant Surgeon, United States Public Health Service.

Between the identification of the *Bacillus pestis* as the specific cause of bubonic plague and the full recognition of the rôle played by rats and fleas in its dissemination, there intervened a period of about 10 years, during which the ravages of a widespread pandemic concentrated the attention of many of the most eminent scientists upon the problems of the prevention and cure of this most fatal disease.

The literature of those years is full of reports upon studies of plague from every point of view—studies of its bacteriology and pathology, its clinical aspects, its epidemiology, and of the efficiency of the preventive measures so laboriously, if often ineffectually, carried out. The inefficiency of eradicative measures, which at that time were based largely upon the belief that human cases were the important sources of infection, rendered the search for methods of immunization and specific therapy most urgent.

It is the object of this paper to give a brief review of the methods evolved for immunization against plague, a review which is believed to be timely because of the present interest in plague consequent upon its proximity to American ports and because the generally circulated medical literature of the United States contains little on this subject.

No effort has been made to consult or cite original references, except a few of the more important. In the monographs which have been freely used in the preparation of this paper may be found full bibliographies and more detailed discussions of the technical questions involved.

I.

ACTIVE IMMUNIZATION AGAINST PLAGUE.

Any method of active immunization, to be of practical application in human beings, must be not only efficient in conferring immunity, but without danger to life, must give a minimum of discomfort, must be simple in its administration, and not prohibitively expensive. Without undertaking a review of all the methods which have been advocated, the following may be cited as those which have seemed to best meet the conditions:

1. THE USE OF KILLED CULTURES AND THEIR PRODUCTS.

(*a*) Haffkine's method (1, 3)[1]: Haffkine, who was the first to extensively advocate and employ preventive inoculations against plague, prepared his material as follows:

Plague bacilli were grown at a temperature of 25° to 30° C. in large shallow flasks, containing bouillon having on its surface droplets of sterile oil, enabling the bacilli to grow in stalactites dependent from these droplets. Every few days the flasks were agitated, causing the growth to fall to the bottom and allowing a new growth at the top. At the end of six weeks, when a very heavy growth had been obtained, the cultures were heated to 65° C. for one hour or more. After their sterility had been proven by subculture, phenol sufficient to make 0.5 per cent was added as an additional assurance of sterility and to guard against subsequent accidental contamination. The bacterial content of the emulsion was estimated roughly by comparison with a standard test culture.

The dose usually given was, for adults, 2 to 3.5 c. c.; for children under 10 years of age, 0.1 to 0.5 c. c.; for older children, 1 to 2 c. c. Doses much larger than these, namely, 10 to 20 c. c., for adults, were subsequently employed with seemingly better results. It was recommended to give, 10 days after the first injection, a second larger dose.

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[1] The figures in parentheses refer to the references at the end of the article.

The reaction following an injection of Haffkine's virus appears to have been quite variable. Elevation of temperature, general malaise, headache, and local reaction at the site of inoculation were common, but seldom lasting more than 24 hours and rarely severe.

(*b*) The German plague commission, (2) after extended experimental researches, came to the conclusion that the efficacy of Haffkine's preparation was due solely to the killed bacilli present therein. The bouillon, when freed from bacilli, was found to have almost no immunizing properties.

This commission accordingly recommended young agar cultures for use instead of the bouillon cultures employed by Haffkine. They used 48-hour agar cultures of virulent plague bacilli, grown at a temperature of about 30° C. These, after being removed and emulsified in physiologic salt solution, were heated to 65° C. for one hour or longer, after which phenol was added sufficient to make 0.5 per cent. They recommend for an adult dose an amount of the emulsion corresponding approximately to one agar culture.

This preparation has the advantage over bouillon cultures that it is more easily and rapidly prepared; the dose can be more accurately regulated; it is not so subject to contamination, especially with tetanus; it has been found experimentally to confer on laboratory animals a high degree of immunity. Its superior efficiency is believed to be due in part to the fact that the cultures used are actively virulent, whereas the bouillon cultures used by Haffkine are said to lose a great deal of their virulence in the six weeks' cultivation.

(*c*) Lustig and Galeotti (3) have devised a method which they believe to be superior to that of the German commission. Twenty-four-hour agar cultures are scraped off and emulsified in a 0.75 per cent solution of caustic soda, which is kept at about 10° C. for 12 to 24 hours. The emulsion has by that time become opalescent, with a bottom sediment, which is removed by filtration through paper. Acetic acid, added to the filtrate, causes a white, flocculent precipitate, which is filtered off, dried in vacuo, and powdered. For use it may be dissolved in a weak solution of sodium carbonate.

It is claimed for this product, which is considered to be a nucleoproteid derived from the plague bacilli, that its immunizing property is approximately equal to that of killed agar cultures of the bacilli; that the dose can be more accurately measured; that the powder keeps well in all climates; and that the reaction following its injection is less severe.

(*d*) Terni and Bandi (3) have recommended, for active immunization, the peritoneal exudate of guinea pigs, inoculated intraperitoneally with virulent plague bacilli and killed in the terminal stage of infection. The exudate, a more or less viscid, cloudy liquid, is kept in an ice chest one or two days until cultures have shown the presence of living bacilli and the absence of other contaminating bacteria. It is then incubated 12 hours at 37° C. to cause multiplication of *B. pestis*, and heated on 2 consecutive days to 52° C. to kill the plague bacilli without coagulating the albumin. After this it is diluted, according to its consistency, with salt solution, containing 0.5 per cent phenol and 0.25 per cent sodium carbonate.

The authors claimed for this method of immunization that it gave to laboratory animals an active immunity demonstrable within a few hours after inoculation and caused only a mild reaction.

(*e*) Several workers, notably Shiga and Besredka, have made use of killed agar cultures mixed with specific antiplague immune serum, claiming for this preparation an efficacy equal to that of killed cultures alone, and the advantage that the reaction after inoculation is decidedly less severe, and that immunity is established very rapidly without a "negative phase."

2. INOCCULATION WITH ATTENUATED LIVE CULTURES.

It has been shown by numerous observers that inoculation with attenuated or avirulent cultures of plague bacilli will give to laboratory animals an immunity of higher degree and longer duration than that conferred by inoculation with killed cultures or their products. The cultures used have been attenuated by long subculture on artificial media, to which have been added, in some instances, alcohol or other substances unfavorable to the development of the bacilli. Strong (3), using a long-cultivated culture of plague bacilli which he had found harmless but highly immunizing for guinea pigs and monkeys, inoculated 42 condemned criminals in a Manila prison. Some of these, after the preliminary tests of small doses, received as much as a whole agar culture of live bacilli with no harmful effect other than a brief local and general reaction. Immune bodies were demonstrated in the blood of 24 of these patients, and from the results of animal experiments it may be inferred that these people acquired a considerable degree of immunity against plague infection. However, in spite of the demonstrated harmlessness of the method in this series of experiments, it is hardly to be expected that such a procedure will come into general use, for there remains the fear of sometimes using a culture insufficiently attenuated, or of encountering persons peculiarly susceptible to the infection.

3. RESULTS OBTAINED IN ACTIVE IMMUNIZATION AGAINST PLAGUE.

The results obtained by different workers in attempting to compare the efficiency of the several methods of immunization above enumerated are various (1). It seems to be quite generally agreed that inoculation with attenuated living cultures (true "vaccination") gives experimentally more definite and lasting immunity than does inoculation with killed cultures or derivatives. Kolle and Otto (4) found the immunizing effect of Haffkine's preparation and that of the German plague commission approximately equal and that of Lustig and Galeotti somewhat less. They were unable, by any of these methods, to constantly immunize highly susceptible animals (rats and guinea pigs) against experimental infection with virulent plague bacilli. They estimated that in their experiments the immunizing effect on rats was, with living attenuated cultures, 45 per cent; by Haffkine's method, 22.2 per cent; by the German plague commission's method, 21.9 per cent; and by Lustig's, 16.6 per cent. Their results with guinea pigs were even less favorable. A more satisfactory estimate of the practical efficiency of antiplague inoculations may be obtained from a study of the records of the incidence of plague among inoculated and uninoculated persons in plague-stricken communities in India during the last great epidemic there. Since 1897 over a million of people have received antiplague inoculations in India and elsewhere. In most instances it has been impossible to accurately estimate the results obtained because of the impossibility of keeping full records and the difficulty of estimating the influence of environmental factors, or because the incidence of plague among the uninoculated population has been so small that its nonincidence among the inoculated was of doubtful significance. Nevertheless, during the great epidemic in India some tests were made under conditions so well controlled as to warrant quite definite conclusions. A few of these tests may be cited here, from reports by Haffkine, Bannerman, and others.

In the last week of January, 1897, plague appeared in the Byculla house of correction, in Bombay, causing, up to January 30, 9 cases, of which 6 were fatal (1, 5, 7). On the morning of January 30, 6 more cases developed, of which 3 resulted fatally. On the afternoon of this day Dr. Haffkine inoculated all the inmates who volunteered to submit to it. Altogether 154 were inoculated, while 183 refused the offer. The inoculated and uninoculated remained together under the same conditions as regards exposure to infection, food, and work. After the inoculations it was discovered that one of those inoculated had a bubo, and the same evening two more of the inoculated developed plague, all three of these cases proving fatal.

The following table shows the subsequent incidence of plague and deaths therefrom among the inoculated and the uninoculated prisoners. The average daily number of inoculated inmates was 148 and of the uninoculated 173 during this period.

Date.	Uninoculated inmates, 173.		Inoculated inmates, 148.	
	Cases of plague.	Fatal cases.	Cases of plague.	Fatal cases.
Jan. 31	2	1	1	
Feb. 1	1	1		
2	1	1		
3				
4	1	1		
5	2	1		
6	5	1	1	
Total	12	6	2	

NOTE.—In the various reports of this experiment there are slight discrepancies as to the number of inoculated and uninoculated, but all agree as to the incidence of plague.

The last case of plague occurred on February 6. Up to that time there had been among the 173 uninoculated 12 cases of plague with 6 deaths, while among the 148 inoculated there had been exclusive of the 3 sick at the time of inoculation, only 2 cases, both terminating in recovery.

In December, 1897, plague appeared in the Umarkadi jail at Bombay (5, 7). Up to January 1, 1898, there had been 3 cases, all resulting fatally. On this date, the inmates being willing to have the protective inoculation, all were lined up and marched into the yard, where an officer impartially picked out every second man to be inoculated. Special care was taken that the inoculated and the uninoculated should be subjected to identical conditions. The uninoculated were even allowed to rest from work during the period of reaction from the inoculations.

After that date 13 cases of plague appeared during the next 30 days. The average daily number of inoculated inmates during this time was 147, and of the uninoculated, 127. The 13 cases of plague were distributed as follows:

	Cases.	Deaths.
Among 147 inoculated inmates	3	0
Among 127 uninoculated inmates	10	6

At Kirkee, a military suburb of Poona, plague broke out among a colony of native camp followers, living in barracks well isolated from other communities (5, 7). A census showed 1,530 persons—men, women, and children—of whom 671 availed themselves of the offer of inoculation, while 859 persons—members of the same families, living under identical conditions, in the same houses—remained uninoculated. From the time of the inoculation up to the end of the epidemic there occurred 175 cases of plague with 115 deaths. The distribution of cases and deaths among the inoculated and the uninoculated was as follows:

	Cases.	Deaths.	Mortality rate per 100.
Among 671 inoculated	32	17	2.5
Among 859 uninoculated	143	98	11.4

Another test was made in the village of Undhera, near Baroda, where plague broke out in the latter part of December, 1897, causing 76 deaths from plague up to February 12 (5, 7). On this date there were, according to a careful census, 950 people in the village. Of these, 513 were inoculated, leaving 437 uninoculated.

In choosing subjects for inoculation the families were called out from the census records and each divided in such a way as to give an approximately equal proportion of men, women, and children, sickly and strong. Excluding from consideration 3 deaths occurring among the uninoculated from February 12 to 14, inclusive, there occurred in the village 35 cases of plague from February 15 to March 26, after which no further cases occurred. These 35 cases occurred in 28 families, containing 135 persons, of whom 71 were inoculated and 64 uninoculated, as follows:

	Cases.	Incidence per 100.	Deaths.	Deaths per 100.	Case fatality rate per 100.
Among 71 inoculated	8	11.3	3	4.2	37.5
Among 64 not inoculated	27	42.2	26	40.6	96.3

The reduction both in the incidence and in the case mortality among the inoculated is striking. Considering the village as a whole, the incidence among inoculated and uninoculated was:

	Cases.	Incidence per 100.	Deaths.	Mortality rate per 100.
Among 513 inoculated	8	1.5	3	0.58
Among 437 not inoculated	27	6.17	26	5.95

From these figures it appears that the mortality from plague among the total inoculated population was approximately one-tenth that among the uninoculated, the difference being due in part to the less frequent incidence of the disease, and in part to the much lower case mortality among the inoculated.

Many other statistics have been collected by Haffkine, Bannerman, and others, seldom as well controlled as those above cited but tending, almost without exception, to show that inoculation with Haffkine's prophylactic effected a marked but variable reduction in the incidence of plague and the severity of the attack.

The Indian plague commission,[1] while granting that these conclusions are correct, were unable to arrive at a numerical estimate of the protection afforded, and called attention to several shortcomings in the process, namely:

1. The protection is not absolute.
2. The immunity conferred within the first few days is slight and its duration is indeterminable—certainly several weeks, perhaps several months.
3. The lack of any satisfactory method of standardizing the product is a serious obstacle in the way of obtaining uniform results.

It might well be feared that an inoculation during the incubation period would aggravate the severity of the attack, lessening the chances for the patient's recovery. Bannerman has prepared from reports of Government officials the following statistics relative to the case mortality from plague in inoculated persons. His statistics embrace 358 cases of plague developing within 10 days after inoculation and 566 developing later.

Case mortality of plague in persons inoculated with Haffkine's prophylactic [*Bannerman* (7)].

Day after inoculation on which plague developed.	Number of cases.	Number of deaths.	Case mortality rate per 100.
Same day	43	21	48.8
First day after inoculation	40	23	57.5
Second day after inoculation	40	22	55.0
Third day after inoculation	38	21	55.3
Fourth day after inoculation	27	10	37.0
Fifth day after inoculation	37	18	48.6
Sixth day after inoculation	26	10	38.5
Seventh day after inoculation	29	14	48.3
Eighth day after inoculation	24	9	39.5
Ninth day after inoculation	24	15	62.5
Tenth day after inoculation	30	9	30.0
Total to and including the tenth day	358	172	48.04
More than 10 days after inoculation	566	230	40.6
Total among inoculated	924	402	43.5
Total among uninoculated population during same period	5,079	3,728	73.7

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[1] Cited by Dieudonné. Original article not available.

These figures give no support to the theory that it is dangerous to give inoculations to persons in the incubation period of plague. They indicate, rather, that even in such cases inoculation may be of benefit, reducing the severity of the attack.

None of the preparations other than Haffkine's has been tested under circumstances permitting conclusions as to its efficacy in protecting human beings exposed to plague infection. The experimental evidence is, however, sufficient to justify the belief that the killed agar cultures recommended by the German plague commission are as effective as Haffkine's preparation. Concerning the other preparations it is almost impossible to attempt an estimate.

II.

PASSIVE IMMUNIZATION AND SPECIFIC SERUM THERAPY IN PLAGUE.

Yersin, Calmette, and Borrel first showed that the serum of animals immunized against *B. pestis* has protective properties, and Yersin was the first to prepare and use antiplague horse serum, which is still often spoken of as "Yersin's serum."

The serum at present most commonly used is obtained from horses immunized by repeated intravenous injections, first of killed cultures, later of living virulent cultures of *B. pestis* (8).

Modifications of this process are sometimes employed. Lustig's nucleoproteids have been used instead of plague bacilli for immunizing horses; and Markl, in the search for a serum of more markedly *antitoxic* properties, has used filtrates of bouillon cultures for immunizing goats. Terni and Bandi have used the sterilized peritoneal exudate of plague-infected guinea pigs as their antigen. It does not appear to be clearly demonstrated that any of these methods has distinct advantages over the one first mentioned.

The serum so prepared exhibits specific bacteriolytic, bacteriotropic, agglutinative, precipitating, and antitoxic properties. The antitoxic property is apparently weak. It is directed against the endotoxins liberated by the destruction of the bacilli, since *B. pestis* does not excrete a demonstrable soluble toxin.

No method has yet been devised for satisfactorily standardizing the serum. The nearest approximation seems to be attained by testing its protective property in mice.

Experimentally, the serum has been shown to have considerable potency in protecting animals against plague infection when given prior to, coincidentally with, or shortly after inoculation. The passive immunity, conferred by injection of the serum in monkeys, rats, and guinea pigs, appears not to last over 14 days, and to be by no means constant even during that period.

When given after inoculation, the serum has been found much less effective, and when administered after symptoms of sickness have developed it has seldom been found capable of saving the life of an animal inoculated with highly virulent plague.

The results obtained from the use of antiplague serum in the treatment of human plague have been extremely variable, and for the most part disappointing.

In Yersin's first test of his serum, during the epidemic of 1896 in Canton and Amoy, where the general mortality was estimated at 80 to 90 per cent, only two of the 26 patients treated with serum died, a mortality of only 7.6 per cent. In Bombay, in 1897, the mortality among 141 serum-treated cases was 49 per cent, while among 685 cases not so treated it was 80 per cent. In an epidemic at Anam in 1898 the mortality among 33 serum-treated cases was 14, or 42 per cent, while the 39 patients not so treated all died.

In the Vishandi hospital at Karachi the mortality among 288 cases treated before serum was available was 70 per cent. Later, when serum was available, the mortality among 47 serum-treated cases was 47 per cent, while in 74 cases treated without serum during the same period it was 74 per cent. Still later, when the supply of serum was exhausted, the mortality fell to 55 per cent in patients treated without serum.

So, through a long list of statistics, the results ascribed to the use of serum vary from an apparent great saving of life to almost nothing. It is difficult to draw conclusions, because in some instances the cases treated with serum have been selected, moribund cases being excluded; in other instances the comparison has been made between the mortality in cases treated with serum in hospitals and that in cases not treated in hospitals. Further error is introduced by the failure to discover and include in the statistics light cases of plague among the more ignorant classes; and by the variable virulence of the infection at different periods during the same epidemic.

Altogether, it seems impossible at present to make an even approximately accurate estimate of the efficiency of the serum. Yet, in the absence of any other effective therapy, it should undoubtedly be used wherever possible. In mild and moderately severe bubonic cases it may be expected to decrease the severity and duration of illness, and to save some lives. In the very severe bubonic forms its efficiency appears more doubtful, and pneumonic cases may be expected to terminate fatally in spite of the most active serum therapy.

When serum is used it should be administered freely, in doses of 40 to 60 c. c., given wholly or at least in part intravenously, and repeated daily until beneficial results are apparent.

Such figures as have been available relative to the efficacy of antiplague serum as a prophylactic do not appear to be convincing, though the serum has been thought by some to have proven effective. Several instances are cited of persons developing plague from 12 to 20 or more days after having received a prophylactic injection of serum, demonstrating what has been shown by animal experiments, that the immunity conferred is very transitory, as is the case generally with passive immunity.

III.

PRACTICAL APPLICATIONS OF VACCINES AND SERUM IN COMBATING PLAGUE.

The fact that inoculation confers a certain degree of immunity against plague, reducing the chance of contracting the infection and still further reducing the chances of death therefrom, does not of itself imply that this is a measure universally applicable in antiplague campaigns. Other considerations must be taken into account, as, for example, that protective inoculation is at best only a temporary measure, not of plague eradication as we now understand that term, but of plague-prevention in the inoculated individual. Inoculation, even of a whole community, leaves the really important focus of infection—in rodents—untouched, a continued danger to other communities, and eventually, when the immunity has expired, a menace to the same population.

Plague prevention at present has a broader scope than the protection of the particular community where the measures are carried out. The protection of other communities is an equally and often more important object. It is hardly necessary at this day to reiterate that plague prevention in human beings depends above all upon plague eradication in rodents. The realization of this fact, and the demonstrated efficiency of preventive measures based upon it, has relegated prophylactic inoculation to a position of less importance among plague-preventive measures than it occupied 15 years ago, when other measures, based on an imperfect knowledge of the disease, were so distressingly ineffectual.

Inoculation can be at present only supplementary to other more thorough measures of plague prevention. Inoculation en masse will probably continue to be a most valuable adjunct to other measures in communities where plague is extensively and severely epidemic, where there is reason to expect that in the natural course of events the incidence in the total population will be high, and where the social conditions make it impossible to put other measures into immediate effective operation. Such conditions have been in the past encountered in certain communities in India, where 20 per cent or more of the population have been stricken with plague within a few months.

Situations demanding mass inoculations may again be encountered in some countries, but could hardly arise in modern American or European communities where, even in the event of a localized epidemic in an institution or a restricted quarter of a city, so intense as to demand extreme measures, evacuation would doubtless prove more feasible and effective.

Even in groups of people who have been intimately exposed to plague infection inoculation is of doubtful applicability. In such a case it would be preferable to resort to the more rapid means of passive immunization, by the use of antiplague serum, either alone or in connection with inoculation.

The practical application of antiplague inoculation in the prevention of plague in a modern American community is virtually limited to the immunization of those whose work must necessarily expose them to infection; workers in plague laboratories and hospitals, rat catchers, fumigators, etc. To all such, prophylactic inoculations should be administered at least once every six months.

The use of antiplague serum for the immunization of whole communities is altogether impracticable because of its excessive cost, the limited supply available, the short duration of the immunity conferred, and the excessive discomfort and actual danger accompanying the repeated administration of serum at such intervals as would be necessary to maintain an immunity.

The serum has an application as a prophylactic for persons who have already been so exposed to plague infection as to justify a fear of the disease developing within a few days. It would, for example, be administered to the immediate associates of a plague patient when the conditions are such as to make it probable that they have already been infected from the same source or from the patient, and should be administered to those who have wounded themselves while handling plague-infected material.

As a therapeutic agent the serum should be employed freely in all cases of plague as early as possible.

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ANTIRAT ORDINANCE OF OAKLAND, CAL.

[Ordnance No. 2734.—Adopted May 18, 1908.]

AN ORDINANCE PROVIDING FOR THE PREVENTION OF DISEASES, AND FOR THE PROTECTION OF PUBLIC HEALTH, AND PROVIDING A PENALTY FOR VIOLATION THEREOF.

Be it ordained by the council of the city of Oakland as follows, to wit:

SECTION 1. Every person, firm, or corporation owning, occupying, or controlling any wharf, building, or basement in the city of Oakland shall prevent the ingress of rats thereto, and to this end and purpose shall use in the protection of said wharf, building, or basement funnels, screens, netting, cement, or other material, and the method of placing said funnels, screens, netting, cement, or other material shall first be approved by the board of health.

SEC. 2. Every person, firm, or corporation owning, occupying, or controlling any premises in the city of Oakland, county of Alameda, State of California, shall maintain the same in a clean and sanitary condition, and remove therefrom any matter detrimental to health. All food, provisions, goods, wares, and merchandise shall be so located as to prevent rats from gaining access thereto or coming in contact therewith.

SEC. 3. Every person, firm, or corporation owning, occupying, or controlling any premises in the city of Oakland shall place all garbage and waste matters on said premises owned, occupied, or controlled by such person, firm, or corporation, in a metal can, and there shall